NONTECHNICAL ABSTRACT

Herpes Simplex Virus thymidine kinase (HSV1-tk) is an enzyme derived from the Herpes Simplex Virus and is deficient in mammalian cells. HSV1 -tk can metabolize an antiviral drug called ganciclovir into toxic compounds which can kill cells harboring the enzyme as well as neighboring cells. We have shown in animal studies using mice which bear established colon cancers in their livers that an injection into a liver tumor of an adenovirus (a virus which produces symptoms of the common cold) expressing the HSV1-tk gene (ADV-tk or Adv.RSV-tk) and followed by ganciclovir administration resulted in destruction of the injected tumor.

We have tested the safety of intratumoral injection of ADV-tk followed by intravenous ganciclovir in a Phase I clinical trial in patients with metastatic colorectal cancer to the liver. We have found that virus doses of up to 10^{13} virus particles per patient can be safely administered with reversible mild to moderate adverse side effects, such as mildly elevated liver function tests, low while blood cell count and platelet count. Fevers as high as 40.1 degC were seen following virus injection which came back to normal within a few days to one week. The treatment procedures were successful in stabilizing the size of the injected tumor which had been increasing prior to study. The question whether the tumor injected with the adenovirus actually produced the HSV1-tk enzyme and whether the adenovirus was contained within the tumor or has spread to other organs remain unanswered.

We have shown in similar animal studies with mice bearing established colon cancers in the liver that intravenous administration of a compound similar to ganciclovir called FIAU which has been previously labeled with radioactive iodine can detect cells which produces the HSV1-tk enzyme followed intratumoral injection of ADV-tk since the HSV1-tk enzyme was able to metabolize the FIAU and caused it to be retained in these cells. These cells were then detectable by using instruments which detect radioactivity. Using biochemical and molecular biological methods were showed that the areas of radioactivity corresponded to cells which produced HSV1-tk.

We are in a position now to test if intravenous administration of radiolabeled FIAU prior to intratumoral injection of ADV-tk as performed in our previous Phase I trial can detect uptake of the radiolabeled FIAU. We propose a clinical trial which is essentially a continuation of our previous Phase I trial with intratumoral injection of ADV-tk at the highest dose level administered in the previous trial followed by intravenous ganciclovir. This ADV-tk dose level has been shown in the previous trial to be safely tolerated. In the proposed trial, we will administer FIAU which has been radiolabeled with radioactive iodine I-124 prior to and within 24 hours after intratumoral ADV-tk injection. PET scans will be performed followed each I-124 FIAU injection to detect the intensity and distribution of the radiolabeled FIAU. Completion of this trial will help us determine if intratumoral injection of ADV-tk can induce cells to produce HSV1-tk (and detected by I-124 FIAU and PET imaging) and if subsequent treatment with ganciclovir can produce tumor necrosis and stabilization. Four patients will be treated in the proposed trial.